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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,808	11/14/2003	Dave S.B. Hoon	89212.0014	4483

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10 and 31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10 and 31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 7/31/07 in response to the Office Action of 1/31/07 are acknowledged and have been entered.

Claims 1-7, 10, and 31-35 are pending.

Claims 1-4 and 31-35 have been amended by Applicant.

Claims 1-7, 10, and 31-35 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections necessitated by Amendments.

Rejections Withdrawn

The rejections under 35 U.S.C. 112, second paragraph, are withdrawn.

The rejection of claims 1-7, 10, 34, and 35 under 35 U.S.C. 112 first paragraph, for failing to comply with the enablement requirement, is withdrawn. However, it is noted that a new enablement rejection, necessitated by amendments, is set-forth below.

The rejection of claim 35 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement, is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-33 remain rejected under 35 U.S.C. 103(a) for being unpatentable over Palmieri et al (March 2001, Journal of Clinical Oncology, 19(5):1437-1443) in view of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418) for the reasons stated in the Office Action of 1/31/07 and for the reasons set-forth below.

The claims are drawn to methods comprising detecting the mRNA expression of a panel of marker genes comprising GalNAct and/or PAX3 in a SLN sample histopathologically negative for melanoma cells obtained from a melanoma patient.

The Office Action of 1/31/07 contains the following text:

"Palmieri et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase (pages 1438-1439, in particular). The methods taught by Palmieri et al comprise methods wherein the sentinel lymph node samples are histopathologically negative for melanoma cells (paragraph bridging the left and right columns of page 1438), wherein the histopathology is determined by

hematoxylin and eosin staining and immunohistochemistry. Palmieri et al further teaches, and one of skill in the art would recognize, that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells (page 1441 right column, in particular).

Palmieri et al does not specifically teach methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MAGE-A3, GalNAcT and/or PAX3. However, these deficiencies are made up in the teachings of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418).

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX3, MAGE-A3, and tyrosinase and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

Kuo et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising GalNAcT and detecting the presence or absence of GalNAcT (page 413 right column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to detect metastatic melanoma cells comprising

a method of isolating nucleic acids from histopathologically negative sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase as taught by Palmieri et al and also amplify any other genes associated with metastatic melanoma, such as those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT). Further, one would have been motivated to do so because multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since detection of genes is well known and conventional in the art."

In the Reply of 7/31/07, Applicant argues that none of the cited references disclose detection of GalNAcT or PAX3 in histopathologically negative SLN samples. Applicant further states that Examiner's assertion that there would be a reasonable expectation of success in detecting GalNAcT or PAX3 in histopathologically negative SLN samples has no basis in the cited art and there would not have been a reasonable expectation of success in detecting PAX3 or GalNacT in histopathologically negative SLN samples from melanoma patients. Applicant further argues that Palmieri, Scholl, and Kuo do not indicate that GalNAcT or PAX3 would share the same expression pattern as Tyrosinase and MART-1 simply because they are melanoma markers. Applicant further agues that it is well known in the art that not all genes are detectable in all type of samples and that a melanoma marker detected in one type of sample from a melanoma patient is not necessarily detectable in another type of sample from

melanoma patients. Applicant further states that Kuo demonstrates that while GalNAcT is detectable in blood samples form AJCC stage II, III, or IV melanoma patients, it is not detectable in blood samples from AJCC stage I melanoma patients. Applicant further states that detection of PAX3 in cultured primary melanomas and their corresponding tissue sections and the detection of GalNAcT in melanoma cell lines, primary biopsies, histopathologically positive tumor-draining lymph node (TDLN) metastasis, distal organ metastasis, and blood do not indicate that GalNAcT and PAX3 would be detectable in histopathologically negative SLN samples from melanoma patients.

The arguments found in the Reply of 7/31/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that none of the cited references disclose detection of GalNAcT or PAX3 in histopathologically negative SLN samples, the Examiner agrees that none of the cited references disclose detection of GalNAcT or PAX3 in histopathologically negative SLN samples. However, motivation to detect GalNAcT and PAX3 in histopathologically negative SLN samples is discussed above. Specifically, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to detect metastatic melanoma cells comprising a method of isolating nucleic acids from both histopathologically negative and histopathologically positive sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase as taught by Palmieri et al and also amplify any other transcripts of genes expressed by metastatic melanoma cells, such as those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT) and one

would have been motivated to do so because Palmieri et al teaches and one of skill in the art would recognize that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells.

In regards to the argument that Examiner's assertion that there would be a reasonable expectation of success in detecting GalNAcT or PAX3 in histopathologically negative SLN samples has no basis in the cited art, there would be an expectation of success in detecting levels of GalNAcT or PAX3 (both levels indicative of no transcripts and levels indicative of GalNAcT or PAX3 transcripts) because Sholl et al teaches methods of detecting levels of PAX3 transcripts and Kuo et al teaches methods of detecting levels of GalNAcT transcripts.

Further, in regards to the argument that Palmieri, Scholl, and Kuo do not indicate that GalNAcT or PAX3 would share the same expression pattern as Tyrosinase and MART-1 simply because they are melanoma markers and it is well known in the art that not all genes are detectable in all type of samples and that a melanoma marker detected in one type of sample from a melanoma patient is not necessarily detectable in another type of sample from melanoma patients, one of skill in the art would expect differential expression of GalNAcT, PAX3, Tyrosinase, and MART-1 in metastatic melanoma cells because Palmieri, Scholl, and/or Kuo teach that GalNAcT, PAX3, Tyrosinase, and MART-1 are differentially expressed in metastatic melanoma cells (note that metastatic melanoma cells are a single type of sample).

Double Patenting

Claims 1-7, 10, and 31-34 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/227575. Although the conflicting claims are not identical, they are not patentably distinct from each other because both instant claims 1-7, 10, and 31-34 claims 1-16 of copending Application No. 11/227575 are drawn to methods of diagnosis of and prognosis of melanoma using identical markers and identical or obvious samples.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the Reply of 7/31/07, Applicant indicated that an appropriate terminal disclaimer would be provided if the pending claims are found to be otherwise allowable except for this ground of rejection.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 10, 34, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7, 10, 34, and 35 are drawn to methods whereby patients are determined to have increased or decreased probabilities of having various prognoses. However, it is unclear *as compared to what* said probabilities are increased or decreased.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 10, 34, and 35 are rejected under 35 U.S.C. 112 first paragraph, for failing to comply with the enablement requirement, because while being enabling for methods for melanoma prognosis comprising detecting levels of mRNA transcripts encoded by a panel of genes comprising GalNAcT, PAX3 or both, wherein as compared to the levels of mRNA transcripts encoded by said panel in samples from a second melanoma patient, higher levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has an increased probability of metastatic melanoma recurrence as compared to the probability of metastatic melanoma recurrence of the second patient, a decreased probability of metastatic melanoma-free survival as compared to the probability of metastatic melanoma-free survival of the second patient, or a decreased length in overall survival time as compared to the length in overall survival time of the second patient, and lower levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has a decreased probability of metastatic melanoma recurrence as

compared to the probability of metastatic melanoma recurrence of the second patient, an increased probability of metastatic melanoma-free survival as compared to the probability of metastatic melanoma-free survival of the second patient, or an increased length of overall survival time as compared to the length of overall survival time of the second patient, the specification does not reasonably provide enablement for methods for melanoma prognosis comprising detecting levels of mRNA transcripts encoded by a panel of genes comprising GalNAcT, PAX3 or both, wherein as compared to the levels of mRNA transcripts encoded by said panel in samples from a second melanoma patient, higher levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has an increased probability of metastatic melanoma recurrence *as compared to any other probability*, a decreased probability of metastatic melanoma-free survival *as compared to any other probability*, or a decreased *probability of overall survival as compared to any other probability*, and lower levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has a decreased probability of metastatic melanoma recurrence *as compared to any other probability*, an increased probability of metastatic melanoma-free survival *as compared to any other probability*, or *an increased probability of overall survival as compared to any other probability*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods for melanoma prognosis comprising detecting levels of mRNA transcripts encoded by a panel of genes comprising GalNAcT, PAX3 or both, wherein as compared to the levels of mRNA transcripts encoded by said panel in samples from a second melanoma patient, higher levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has an increased probability of metastatic melanoma recurrence, a decreased probability of metastatic melanoma-free survival, or a decreased *probability of overall survival*, and lower levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has a decreased probability of metastatic melanoma recurrence, an increased probability of metastatic melanoma-free survival, or *an increased probability of overall survival.* This includes methods whereby probabilities are determined to be increased or decreased *in comparison to any other probability.* Further, methods comprising determining an increase in probability of overall survival read on methods whereby a subject would either survive indefinitely or not survive.

The specification teaches methods for melanoma prognosis comprising detecting levels of mRNA transcripts encoded by a panel of genes comprising GalNAcT, PAX3 or

both, wherein as compared to the levels of mRNA transcripts encoded by said panel in samples from a second melanoma patient, higher levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has an increased probability of metastatic melanoma recurrence as compared to the probability of metastatic melanoma recurrence of the second patient, a decreased probability of metastatic melanoma-free survival as compared to the probability of metastatic melanoma-free survival of the second patient, or a decreased length in overall survival time as compared to the length in overall survival time of the second patient, and lower levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has a decreased probability of metastatic melanoma recurrence as compared to the probability of metastatic melanoma recurrence of the second patient, an increased probability of metastatic melanoma-free survival as compared to the probability of metastatic melanoma-free survival of the second patient, or an increased length of overall survival time as compared to the length of overall survival time of the second patient (see pages 25-30 and Figures 4-5, in particular).

The state of the prior art dictates that if levels of molecules such as a PAX-3 transcripts are to be used to determine a particular prognosis, some particular prognosis must be identified in some way with levels of the molecule. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish

quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

The level of unpredictability for using levels of a particular molecule to determine a particular prognosis is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the probabilities of the particular prognoses recited in the claims and every other probability, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive. Further, one of skill in the art would recognize that a subject would not survive

indefinitely. Therefore, methods of determining a probability of "overall survival" would not function as claimed.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods for melanoma prognosis comprising detecting levels of mRNA transcripts encoded by a panel of genes comprising GalNAcT, PAX3 or both, wherein as compared to the levels of mRNA transcripts encoded by said panel in samples from a second melanoma patient, higher levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has an increased probability of metastatic melanoma recurrence, a decreased probability of metastatic melanoma-free survival, or a decreased *probability of overall survival*, and lower levels of mRNA transcripts encoded by the panel in samples from a first patient indicate that the first patient has a decreased probability of metastatic melanoma recurrence, an increased probability of metastatic melanoma-free survival, or *an increased probability of overall survival*, and Applicant has not enabled said methods because it has not been shown that higher levels of mRNA transcripts encoded by the panel in samples from a first patient, as compared to the levels of mRNA transcripts encoded by said panel in samples from a second melanoma patient, indicate that the first patient has an increased probability of metastatic melanoma recurrence as compared to every other probability of every other patient, a decreased probability of metastatic melanoma-free survival as compared to every other probability of every other patient, or a decreased *probability of overall survival* as compared to every other probability of every other patient, and lower levels of mRNA transcripts

encoded by the panel in samples from a first patient indicate that the first patient has a decreased probability of metastatic melanoma recurrence as compared to every other probability of every other patient, an increased probability of metastatic melanoma-free survival as compared to every other probability of every other patient, or *an increased probability of overall survival* as compared to every other probability of every other patient. Further, it has not been shown that metastatic melanoma patients could survive indefinitely.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Summary

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action

is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

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